polyoxyethylene sorbitan monooleate [Tween 80®], and 0.5% w/v sorbitan trioleate [Span 85®], and optionally, N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(l'-2'-dipalmitoyl-*sn*-glycero-3-huydroxyphosphoryloxy)-ethylamine, and (b) a selected antigen entrapped in, or adsorbed to, a poly(D,L-lactide-co-glycolide) microparticle.

Please cancel claims 6, 7 and 14-27 without prejudice and disclaimer.

REMARKS

Introductory Comments:

Claims 1-5, 8-13 and 28-30 were examined in the Office Action dated August 25, 1999 and rejected under (1) 35 U.S.C. §112, second paragraph as indefinite (claims 4 and 11); (2) 35 U.S.C. §102(e) (claims 1-3, 5, 9, 10 and 28-30); and (3) 35 U.S.C. §103 (claims 1-5, 8-13 and 28-30). These rejections are believed to be overcome by the above amendments and are otherwise traversed for reasons discussed below.

Overview of the Above Amendments:

The specification has been amended, as requested by the Office, to capitalize trademarks.

Claims 6, 7 and 14-27 have been canceled as drawn to a non-elected invention. Cancellation of these claim is without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to bring the canceled claims again in a subsequent application.

Claims 4 and 11 have been amended as requested in the Office Action in order to recite the invention with greater particularity. Specifically, the terms "Tween 80®" and "Span 85®" have been replaced with the terms "polyoxyethylene sorbitan monooleate" and "sorbitan trioleate," respectively. Support for these amendments can be found in the claims as filed as well as throughout the specification at, e.g., page 22, line 33 to page 23, line 4. See also pages 957 and 1807 of the *Sigma Catalog: Biochemicals and Reagents*

for Life Science Research (1999) which details the chemical name for Tween and Span. Additionally, claims 1 and 11 have been amended to specify that the submicron oil-in-water emulsion is an immunological adjuvant. Support for this amendment can be found throughout the specification, at e.g., Example 2 at pages 29-30 and Examples 4-6, at pages 32-37. Accordingly, no new matter has been added to the application by way of the above amendments and new claims.

Rejections Under 35 U.S.C. §112, Second Paragraph:

Claims 4 and 11 were rejected as indefinite under 35 U.S.C. §112, second paragraph. The Office requested clarification with respect to the trademarked names for chemical reagents. As discussed above, claims 4 and 11 have been amended per the Examiner's suggestions. Particularly, the terms "Tween 80®" and "Span 85®" have been replaced with the terms "polyoxyethylene sorbitan monooleate" and "sorbitan trioleate," respectively. Thus these basis for rejection has been overcome. Withdrawal of the rejections under 35 U.S.C. §112, second paragraph is therefore respectfully requested.

The Rejection under 35 U.S.C. §102(e)

Claims 1-3, 5, 9, 10, and 28-30 were rejected under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 5,869,103, issued to Yeh et al. ("Yeh"). In support of the rejection, the Office asserts that "Yeh discloses lactide and glycolactide copolymer microparticles comprising various antigens, suspended in various adjuvants, including oil-in-water adjuvants" wherein the antigen can be a viral antigen. Office Action, page 4. Applicants respectfully traverse these rejections and submit that the claims distinguish over the cited art.

Anticipation of a claim under §102 *requires* each and every element as set forth in the claim to be disclosed in a *single* prior art reference (*Davis v. Loesch*, 27 USPQ2d 1440 (Fed. Cir. 1993)). Additionally, exclusion of a single claimed element from a prior art reference is enough to negate anticipation by that reference (*Atlas Powder Co. v E.I.*

du Pont De Nemours & Co. 224 USPQ 409, 411 (Fed Cir. 1984)). Thus, applicants submit that the rejection of claims 1-3, 5, 9, 10, and 28-30 over Yeh is improper.

In particular, claim 1 (from which claims 2, 3, 5, 9 and 10 depend), claim 11 and claim 28 (from which claims 29 and 30 depend) recite a composition and a method of making a composition, respectively, comprising a submicron oil-in-water emulsion immunological adjuvant, and a selected antigen entrapped in, or adsorbed to, a biodegradable microparticle. The claimed biodegradable microparticle is formed from a poly(α-hydroxy acid) selected from the group consisting of poly(L-lactide), poly(D,L-lactide) and poly(D,L-lactide-co-glycolide). In contrast, the microparticles discussed in Yeh, formed from a mixture of a biodegradable polymer, such as polylactide, polyglycolactide, copolymers of α-hydroxy acid and α-amino acid (see column 3, line 56 to column 4, line 3), and a water soluble polymer, such as PEG, PEO, PEO-PPO (see column 4, lines 4-33), wherein the ratio of the biodegradable polymer to the water-soluble polymer ranges from 99:1 to 10:90. Additionally, the microparticles disclosed by Yeh, have a size ranging from approximately 7-30 μm (see Tables 1-9 at columns 8-13). Thus, the microparticles discussed in Yeh are distinct from the claimed biodegradable microparticles. Contrary to the Office's assertion, Yeh makes no mention of any formulations or adjuvants, the reference simply mentions various modes of administration. Yeh only mentions that preferably the active agent is water-soluble (see column 5, lines 26-29). Further, Yeh discloses standard methods of making micorparticles using emulsion/solvent evaporation techniques, wherein the primary emulsion, i.e., oil-in-water (W/O) emulsion, is further manipulated to yield the secondary emulsion (W/O/O) (see column 7, lines 32-47). Yeh does not mention a composition comprising a submicron oil-in-water emulsion immunological adjuvant, and a selected antigen entrapped in, or adsorbed to, a biodegradable microparticle, as claimed.

Applicants have disclosed and claimed a composition and a method of making the composition which contains recited elements that are not disclosed in Yeh. Thus applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 5, 9, 10, and 28-30 under 35 U.S.C. §102(e).

Rejections Under 35 U.S.C.§ 103(a)

Claims 1-5, 8-13 and 28-30 were rejected under 35 U.S.C. §103(a), as unpatentable over Esparza et al (*Vaccine*, 1992, 10:714-720) ("Esparza") in view of Higgins et al. (*Vaccine*, 1996, 14:478-484) ("Higgins"). Applicants respectfully traverse these rejections and the supporting remarks for the following reasons.

The Office asserts that Esparza discloses immunogenic PLA:PGA micorparticles comprising an antigen in water-in-oil suspension (emphasis added). Further, the Office asserts that Esparza concludes that a vaccine composition containing the microparticles and the adjuvant induces a secondary antibody response. However, the Office acknowledges that Esparza does not disclose oil-in-water emulsions (emphasis added). Office Action, page 5. Additionally, the Office asserts that Higgins discloses an oil-in-water adjuvant (MF59) and its adjuvant properties in viral vaccines, such as HIV and HCV. Office Action, page 5. Thus the Office alleges that "taken together, the instant invention appears to be the same or slightly different from the prior art of evaluating the efficacy of various adjuvants, alone or in combination, for optimization of a vaccine formulation." Office Action, page 5 (emphasis added).

The Office concludes that one of skill in the art would have been motivated to evaluate the efficacy of various adjuvants as part of a vaccine composition, to increase the immune response to an antigen. The Office alleges that it would have been obvious to one of skill in the art to combine the teachings of Esparza with Higgins and have a reasonable expectation of success in producing the claimed invention. Office Action, pages 5-6. However, applicants disagree with these assertions.

It is well settled that for purposes of 35 U.S.C. §103, the differences between the prior art and the claims are not determined based on whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. MPEP §2141.02 citing *Stratoflex, Inc. v. Seroquip Corp.*, 218 USPQ 871 (Fed. Cir. 1983) and *Schenck v. Northon Corp.*, 218 USPQ 698 (Fed. Cir. 1983) (emphasis in the original). Additionally, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is

some teaching, suggestion or motivation to do so found in either the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992). Further, the fact that references can be combined or modified or that the claimed invention is well within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); *Ex parte Levengood*, 28 USPQ2d 1300 (BPAI 1993).

Applicants respectfully submit that the invention as a whole is not obvious and that there is no suggestion to combine the teachings of the art as asserted. In particular, the pending claims pertain to a composition and a method of making the composition comprising a submicron oil-in-water emulsion immunological adjuvant, and a biodegradable microparticle comprising a selected antigen entrapped in or adsorbed thereto. As acknowledged by the Office, Esparza does not disclose a composition comprising an oil-in-water emulsion and a microparticle containing an antigen entrapped in or adsorbed thereto. Esparza discloses Tetanus Toxiod (TT) entrapped in PLA:PGA micorparticles suspended in water-in-oil emulsion (see Abstract). Esparza teaches that primary antibody response against microencapsulated TT was not as prominent when the microparticles were suspended in an oil suspension; while pronounced adjuvant effects of water-in-oil emulsions were observed during secondary antibody response. (See page 719, column 1). Additionally, Esparza discloses that microparticles suspended in an aqueous solution increased the immunogenicity of the antibody after boosting. (See Page 719, column 1). Thus applicants submit that Esparza actually teaches away from a composition comprising an oil-in-water emulsion and biodegradable microparticles comprising a selected antigen as claimed.

Additionally, Higgins although disclosing the use of MF59 as an adjuvant, does not suggest, or provide any incentive to use the claimed composition comprising an oil-in-water emulsion, and a selected antigen entrapped in or adsorbed to, a biodegradable microparticle, to further improve the immunogenic response of the antigen. The present invention is based on the surprising and unexpected discovery that the use of

biodegradable microparticles comprising entrapped or adsorbed antigen, in combination with submicron oil-in-water emulsions, serves to enhance the immunogenicity of the antigen. As demonstrated in the Examples, the immunogenicity of the antigen-entrapped microparticle with MF59 is significantly greater than the nonentrapped antigen with MF59. (See, e.g., Example 2 on pages 29-30 and Examples 4-6 on pages 32-37). The references cited by the Office disclose only selected bits and pieces of the claimed invention. Moreover, as acknowledged by the Office, the instant invention differs from the prior art of evaluating the efficacy of various adjuvants for optimization of a vaccine formulation. (Office Action, page 5). Applicants submit that Esparza actually teaches away from a composition comprising an oil-in-water emulsion and biodegradable microparticles comprising a selected antigen as claimed. Thus applicants submit that there is no suggestion or incentive to combine Esparza and Higgins. Nevertheless, the Office has selected MF59 from Higgins and substituted it in Esparza's disclosure, even though Esparza teaches that microparticles suspended in an aqueous solution improved immunogenicity. The Office has picked and chosen among the references based on applicants' teachings and relied on the use of prohibited reconstructive hindsight to formulate the present rejection. *Symbol Technologies, Inc. v. Opticon, Inc.*, 19 USPQ2d 1241 (Fed. Cir. 1991; *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); and *In re Sernaker*, 217 USPQ 1 (Fed. Cir. 1983). Such combination is therefore inappropriate. Hence, applicants submit that a *prima facie* case of obviousness has not been established and that this basis for rejection should be withdrawn.

For all of the foregoing reasons, applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

Applicants respectfully submit that the claims are novel and nonobvious over the art and comply with the requirements of 35 U.S.C. §112. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

Please direct all further communications in this application to:

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